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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

LEE,G

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE

Office Action Summary

Application No.	Applicant(s)
09/091,605	Borts et al.
Examiner	**Group Art Unit**
Gai (Jennifer) Mi Lee	1632

☒ Responsive to communication(s) filed on Sep 19, 2000

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 19-34 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 19-34 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Arguments

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Note, applicants have canceled claims 1-18 and added new claims 19-34. Thus, applicants have not amended claims 1-18.

Claims 19-34 are currently pending in the instant application.

Priority

The application in which the benefits of an earlier application have been amended to contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78) filed September 19, 2000 in Paper No. 7.

Specification
Arrangement of the Specification

It is noted that Applicants have amended the specification with the proper arrangement of the specification for patent applications filed September 19, 2000 in Paper No. 7.

Claim Objections

Objection of claims 14-15 under 37 CFR 1.75(c) are withdrawn in view of Applicant's amendment and cancellation of the claims filed September 19, 2000 in Paper No. 7.

Claim 34 is objected to because of the following informalities: Claim 34 is claiming dependency to claim 1 which is now canceled or deleted as requested by Applicants filed September 19, 2000. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The prior rejection of claims 1-13 and 16, originally filed or newly added of claims 19-34 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for the following reasons of record.

Claims 19-34 are drawn to a host cell and method of treating Type I or Type II diabetes in a mammal in need thereof comprising injecting an expression vector directly into the mammal such that the expression vector is incorporated into the cell of the mammal and secretes a protein of SEQ ID NO: 1, *in vivo* or *ex vivo*, implanting the host cells transformed with a vector comprising a promoter driving the expression of a DNA sequence encoding a protein of SEQ ID NO: 1.

Applicants argue that the amended claims are directed primarily to cell lines that can be used for *ex vivo* gene therapy. Applicants assert that claims 33-34 are directed to a method of treating diabetes using *ex vivo* or *in vivo* gene therapy. Applicants argue that the state of the art cited in the previous Office Action does not highlight the unpredictability of the gene therapy art because at the time of filing the present application, it had been 7 years since the first human subject underwent gene therapy for the treatment of severe combined immunodeficiency. Applicants argue that the cited references of Ledley and Crystal provide numerous specific

evidences of success for gene transfer feasibility. Further, Applicants argue that diabetes are not generally deficient with respect to endogenous GLP-1 production and thus, the goal is not to replace a defective gene but only to increase the levels of GLP-1 normally present. Thus, the hurdles cited are not hurdles for the present invention. Applicant's arguments filed September 19, 2000 have been fully considered but they are not persuasive.

Applicant's claims are directed to a method of treating Type I or Type II diabetes in a mammal in need thereof comprising implanting host cells or injecting an expression vector directly into the mammal such that the expression vector is incorporated into a cell of the mammal and secretes a protein of SEQ ID NO: 1. However, Applicant's specification fails to teach that which is encompassed in the breadth of the claimed invention as to the unpredictability of gene therapy *in vivo* or *ex vivo* and gene transfer for a stable expression or any expression of the protein in a mammal in order to treat Type I or Type II diabetes. Because the claims are to treatment, treatment encompasses a therapeutic effect or an amelioration of the Type I or Type II diabetes. Expression or *in vitro* expression levels, alone, do not demonstrate the therapeutic effect as claimed to treatment. Further, as asserted by Applicant, the claims embrace both *in vivo* and *ex vivo* methodology of gene therapy. The specification fails to teach the routes of administration, targeting to supply therapeutic treatment nor any dosage or level of expression for treatment of in any and all mammals suffering from Type I or Type II diabetes. Example 7 only demonstrated Applicants implantation of the 293 cells transformed with SEQ ID NO: 1, however, no expression or any correlation could be drawn from the example to demonstrate a

therapeutic effect of such implants to a mammal suffering from Type I or Type II diabetes could be concluded. Thus, as reiterated from the previous Office Action, the claims are still not enabled as the specification does not provide guidance as to the dosage amounts, dosage frequencies, modes of delivery, appropriate expression levels and targeting to supply therapeutic treatment to diabetes or predictably without undue experimentation such that one could induce treatment to any and all Type I or Type II diabetes. While applicants description teaches the skilled artisan how to make the claimed compositions, the description fails to provide guidance to the skilled artisan on how to use the claimed compositions for carrying out the claimed methods of gene therapy. In particular, no protocol is described in the specification comprising administration of cells transformed with a vector comprising a promoter and DNA expressing glucagon like proteins for treatment of the instant invention. Pages 11-22, of the specification, teach the description to the construction of the vector encoding GLP-1 protein of pGT-h+tLB+GLP-1 and pGT-h+tLB+Val8GLP-1. The specification contemplates a number of well known methods that exist for introducing the genetic material into target cells but the specification does not provide any teaching or evidence for therapy. However, the specification does not provide sufficient guidance as to the appropriate route of administration of the cells or vectors for treating diabetes or the appropriate concentration of cells or vectors for any treatment of that one of ordinary skill in the art could reproducibly and consistently effectively treat the patient in need thereof without undue experimentation.

With regards to the cited references showing the unpredictability of the gene therapy as a whole, even though, it has been 7 years since the filing of the instant applications, the unpredictability of the state of the art is still being questioned. Ledley and Crystal both review the hurdles and concerns of the applicability of gene therapy in such limitations of targeting to specific cells, routes of delivery both *ex vivo* and *in vivo*, host immune response to such administration of both viral, non-viral vectors and cells, gene transfer, stability of expression in target cells are still in need to be further addressed specifically in *in vivo* application of gene therapy. As reiterated from the previous Office action, the achievement of therapeutic results by gene therapy, the art as a whole found this to be unpredictable. Blau et al. stated that the main challenge in gene therapy is the achievement of efficient vector delivery and gene expression (Blau et al (1995), page 1204, col. 1-2 bridg. Sent. And page 1205, col. 1-2 bridg. Sent.). Miller et al (1995) that before gene therapy is an option for treating genetic diseases, there is a requirement to produce vector systems that can deliver therapeutic genes to the appropriate target cells either in vivo or ex vivo accurately and efficiently (page 190, col. 1, parag. 1, lines 1-7). Verma et al (1997) states that gene delivery is the "Achilles heel" of gene therapy, and that the ability to deliver and expression genes efficiently to obtain sustained expression is needed for effective therapy (page 239, col. 3, parag. 1.). Ross et al (1996) state that the technical impediment to gene transfer (as a therapy) is the lack of vector systems, and that unless it is possible to deliver the gene to the appropriate blood or body cells and in sufficient quantities, gene therapy will not be efficacious (page 1782, col. 2, parag. 1, lines 1-4). Moreover, in the

"Report and Recommendations of the Panel to Asses the NIH Investment in Research on Gene Therapy" (published December 7, 1995), Orkin and Motulsky indicate that clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol; that major difficulties of gene therapy include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host; that it is not always possible to extrapolated directly from animal experiments to human studies; and that while the most straight-forward application of gene therapy may be in the treatment of single-gene inherited disorders, practical difficulties need to be address, i.e. delivery of the appropriate gene to a specific cell type or tissue, gaining access to the relevant cell type for correction of the defect, assessing the total fraction of cells in a tissue that need to be corrected, achieving the level of expression required for correction, and regulating expression of the added gene once it is transferred into appropriate target cells (see, e.g. pages 1 and 2, points 2,3, and 5, for example, page 5, under "Single-gene inherited disorders", and page 14, bullet parag. 3-6).

With regard to *ex vivo* gene therapy strategies from treating diseases, the specification is non-enabling as the specification does not provide sufficient guidance as to how one of ordinary skill in the art would treat a patient having the disclosed diseases by administering genetically altered cell. The specification does not teach any methodology associated with such treatment regimen including the number of cells to be administered, the route of administration, or the relevant cell therapy target site for treating diabetes. Moreover, the state of the art at the time of filing suggests that cell transplantation therapies to treat any diseases or disorders are neither

routine nor predictable. As to the achievement of treating diabetes using the methods of the instant invention, the art as a whole found this to be unpredictable of the glucagon like proteins efficacy on the treatment of diabetes. Holst et al (1998) state that because of rapid and extensive metabolization, the peptide is not immediately clinically applicable and , as a therapeutic principle, GLP-1 is still in its infancy (p. 336, abstract). Haak, T (1999) teaches that unfortunately, the idea the GLP-1 is superior to all other currently available antidiabetic substances, except insulin, is clouded by the extremely short half-life of less than 2 minutes *in vivo* and that intensive research in the interesting field of the potential therapeutic application of glucagon-like peptide action suggests that answers to many of the unsolved problems will soon be forthcoming (p. S111, col. 1, parag. 1).

Further, Applicants argue that GLP-1 that is administered by subcutaneous or i.v. injection has the effect of enhancing insulin secretion and inhibiting glucagon as well as other effects. Thus, even a small increase in GLP levels can be beneficial to a person with hyperglycemia as long as GLP is secreted into the blood from an implanted expressing cell or a cell transformed in vivo, it will have the desired effect of reducing glucose levels. Applicants further argue that both native GLP-1 as well as the GLP-1 analogs encompassed by the present invention have therapeutic value. Despite this short half-life, native GLP-1 is clearly efficacious especially when administered by continuous infusion. Thus, Applicants assert that efficiency with respect to number of expressing cells transfected *in vivo* is not critical for the present

invention to have value from a therapeutic standpoint. Applicant's arguments have been fully considered but they are not persuasive.

Applicant's specification fails to teach the claimed methods with regards to the routes of administration, targeting to supply therapeutic treatment nor any dosage or any level of expression for treatment of in any and all mammals suffering from Type I or Type II diabetes. The specification fails to teach the limitations discussed above with regards to therapy *in vivo* or *ex vivo*. Example 7 (page 22) only demonstrated Applicant's implantation of the 293 cells transformed with SEQ ID NO: 1, however, no expression nor any correlation could be drawn from the example to demonstrate a therapeutic effect of such implants to a mammal suffering from Type I or Type II diabetes could be concluded.

It is noted that Applicants have not address the issues of relevant animal models and thus, reiterated. Another issue is the relevant animal models which is supported by the teachings of Orkin et al (p. 10 and 13). Orkin stress the importance of using relevant animal models for determining the effectiveness of therapeutic methodologies. Applicants description does not provide any evidence that animal models available to the skilled artisan would provide a reasonable nexus to that of human diabetes. The specification on page 22 teaches transformed 293 cells were surgically transplanted under the kidney capsule of 8 week old Zucker Diabetic Fatty male rats by administering with a 23 gauge blunt needle (lines 19-28). No results on the effectiveness of this implant would have on the rat or the implication toward the treatment of human diabetes.

Thus, it would have required undue experimentation for the skilled artisan to practice the claimed invention in light of the unpredictability of gene therapy, the lack of teachings for parameters to practice the claimed invention in the description, the absence of working examples in the description, the absence of teachings in the art, and the breadth of the claims. Therefore, for the reasons discussed above, the rejection under 35 U.S.C. 112, first paragraph is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

Rejection of claims 1 and 16, originally filed or newly added claim 20 under 35 U.S.C. 112, second paragraph are maintained for the following reason of record.

Claim 20 still contain the terms "immunologically isolated", but the definition provided in Applicant's specification discloses that because such transformed cell lines generally will be histologically incompatible with individuals receiving them, the cells must be protected from the recipient's immune system by masking them with F(ab')2 fragments specific for HLA class I antigens. However, such is not claimed by the instant invention. The claims embraces other aspects of immunologically isolated without such masking or protection of the implanted cells. Thus, the words "immunologically isolated" are still vague and indefinite such that the metes and bounds of the claims can not be readily established as to what would be entailed or how is the isolation accomplished from the mammal's immune system?

Rejection of claims 1 and 16 under 35 U.S.C. 112, second paragraph are moot in view of applicant's cancellation of the claims filed September 19, 2000.

Rejection of claim 10 under 35 U.S.C. 112, second paragraph are moot in view of applicant's cancellation of the claims filed September 19, 2000.

Rejection of claims 16-18 under 35 U.S.C. 112, second paragraph are moot in view of applicant's cancellation of the claims filed September 19, 2000.

Rejection of claim 18 under 35 U.S.C. 112, second paragraph is moot in view of applicant's cancellation of the claims filed September 19, 2000.

Claims 33 and 34 are incomplete. While all of the technical details of method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is practiced. The method of claims 33 and 34 are missing process steps. The method step needs to recite back to the preamble because it is unclear how injecting or implanting correlates to treating Type I or Type II diabetes.

Claim Rejections - 35 USC § 102

The prior rejection of claims 14-15 and 17-18 under 35 U.S.C. 102(b) as being clearly anticipated by Hilliker et al (WO 90/01540) are moot in view of applicant's cancellation of the claims filed September 19, 2000.

The claims are free of the prior art of record.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on 703-305-6608. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

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